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The enigma of young age

Breast cancer in very young patients has traditionally been considered as particularly aggressive and associated with a poor prognosis. The negative prognostic impact of young age has been substantiated in numerous studies of clinical databases [1–4] including a recent population-based analysis of patients with stage I breast cancer: After adjusting for tumor size, histological grade, estrogen receptor (ER) expression, and year of diagnosis, the age at diagnosis was still a significant predictor with each year younger than 45 years adding a relative 5% to the risk of death from breast cancer [5]. The distinction between young and 'very young' premenopausal patients is fuzzy but most investigators who chose to dichotomize their analysis used an age limit of 35–40 years.

It appears obvious that age by itself cannot explain the less favorable outlook of young patients with breast cancer but rather that age is a surrogate for biological features that determine the more aggressive behavior of breast cancers in young women. Indeed, it is a common feature of most studies investigating known prognostic factors in young women to find higher proportions of poorly differentiated, rapidly proliferating, ER- and progesterone receptor (PgR)-negative tumors that tend to be larger and to involve regional lymph nodes [3, 6, 7]; similarly, bone marrow micrometastases, another negative prognostic factor, are observed more frequent in young patients [8]. In some of these analyses, multivariate modeling eliminated age as an independent prognostic factor [6, 9] but in many others the known biological factors did not completely explain the higher likelihood of local [10] and distant recurrence conferred by young age [3, 4, 11].

The interpretation of such retrospective data is confounded by adjuvant therapies that modify the natural course of breast cancer and by temporal changes in the use of such therapies. For instance, the gradual reduction of breast cancer mortality from 1988 to 1997 observed in a recent analysis of SEER data for patients younger that 45 years with stage I breast cancer [5] could result from increased use of adjuvant systemic therapies in the same time period. Indeed, the historically poor prognosis may be related to inadequate therapy as illustrated by data from Denmark on the basis of a population of patients who were diagnosed with breast cancer from 1978 to 1996. Young patients who did not receive adjuvant systemic therapy due to apparent low-risk disease had a much higher probability of recurrence than older patients with otherwise similar characteristics. This negative impact of young age was not observed in patients with higher risk breast cancer who did receive adjuvant systemic therapy. While the use of chemotherapy without hormonal therapy would be considered substandard today, the omission of systemic therapy for very young, seemingly low-risk patients might have contributed to the poor prognosis [12].

Adjuvant chemotherapy may act on at least two general pathways: direct cytotoxic effects in cancer cells and endocrine effects. While cytotoxicity is likely the main mechanism of action in breast cancers that do not express ER and PgR, the suppression of ovarian function by chemotherapy may be the principal mode of action in ER-positive disease: continuing menses is a strong predictor of an unfavorable outcome both after CMF-based [13–16] and after anthracycline-containing chemotherapy [17]. Obviously, the probability of developing amenorrhea depends on the age of the patient and on the regimen used [18]; it is therefore not possible to separately assess the effects of age and of amenorrhea. However, the suppression of ovarian function for at least 2 years has been found to be at least as effective as CMF- and epirubicin-based chemotherapy *without endocrine therapy* in at least eight randomized controlled trials [19]; none of these trials reported differential effects of endocrine or chemotherapy by age, although some confirmed an inferior prognosis for very young patients [15].

Tamoxifen reduces the risk of relapse and death from ER-positive breast cancer; its efficacy does not depend on age and is not diminished by prior chemotherapy [20–22].

Given these complexities, what does the paper reported by authors of the European Institute of Oncology add? Colleoni and et al. [23] have analyzed their prospectively collected database of 841 premenopausal patients treated at their institution for node-negative breast cancer, and they compared the prognostic factors, treatments, and outcomes between very young (below 35 years of age) and older premenopausal patients. As compared to previously reported series, their data are derived from a relatively recent period such that the treatments used are still relevant for today's practice. Unfavorable prognostic factors were more common in tumors of very young patients as expected from other patient series. Despite a relatively standardized therapeutic approach including hormonal therapy for the very young patients with ER-positive tumors, the very young patients were still found to have a significantly higher risk of relapse and death than older patients. This was especially true for patients with ER-positive tumors who did not receive appropriate adjuvant therapy; this observation, while biologically plausible, is based on a subgroup of 18 patients, such that firm conclusions cannot be drawn. Multivariate analyses of survival did not eliminate age as a prognostic factor despite adjusting for tumor size, vascular invasion, proliferation fraction, ER and PgR, and overexpression of HER-2 protein.

Thus, even in a relatively recent population of patients with node-negative early breast cancer that was diagnosed and treated in a reasonably short time period at a single institution, the typical prognostic factors did not fully explain the negative impact of young age. Recently, the development of high-throughput molecular methods has enabled researchers to establish prognostic RNA expression profiles. Several groups have demonstrated that such profiles were able to predict the outcome of breast cancer more accurately than traditional prognostic factors [24–26]. Of particular interest in this context is the analysis of van de Vijver et al. [25]: The proportion of patients with a poor-prognosis gene signature was inversely correlated with age; such signatures were most frequently observed among the youngest women. While young age was a negative prognostic factor on univariate analysis, it was not an independent factor in a multivariate analysis including the gene signature. While similar results have been reported by using the more traditional Nottingham prognostic score [27], the molecular approach offers the potential to investigate the specific mechanisms of carcinogenesis leading to breast cancer at a very young age and to develop therapies that target the involved molecular aberrations. In this context, a recent publication from the Amsterdam group deserves to be mentioned as an example: Dai et al. [28] demonstrated in an analysis of 311 breast cancer samples that while there is on average a positive correlation of ER expression with age, there is a subpopulation of young women whose cancers express a particularly high level of ER for their age. The cancers of this subgroup have a poor prognosis and are characterized by a strong expression of cell cycle-associated genes [28]. While these findings cannot yet be translated directly into therapeutic recommendations, they offer a first molecular clue as to why very young patients with ER-positive breast cancer tend to have a worse prognosis than patients with ER-negative disease as observed by Colleoni et al. [23] in patients who did receive appropriate therapy as well as by other groups in young patients who were treated with chemotherapy but without adjuvant hormonal treatments [29].

The question why breast cancers in very young patients, in particular below the age of 35–40, tend to carry a poorer prognosis than in older patients remains unanswered; as a logical consequence, there are no therapies that are specifically tailored to the characteristics of such tumors with the exception of conventional hormonal agents for patients with ER- or PgR-positive breast cancer. Studies with conventional prognostic factors have exhausted their potential, and any progress will be based on the investigation of molecular events leading to and promoting the development of breast cancer. In the meantime, the best therapy for very young patients is in the framework of a clinical study such as SOFT, TEXT, or PERCHE (http://www.ibcsg.org).

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